October 6, 2000

Ronald L. Joiner, Ph.D.
Manager, Global Toxicology
General Electric Company
One Plastics Avenue
Pittsfield, MA 01201

Dear Dr. Joiner:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for *tris*-Nonylphenyl phosphite (CAS # 26523-78-4), submitted May 25, 2000. I commend the Phosphite Producers HPV Consortium for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program Web site EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the Chemical RTK Web site within the next few days.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
C. Auer
N. Patel
A. Abramson

EPA Comments on Chemical RTK Challenge Submission:

Tris(Nonylphenyl) phosphite

SUMMARY OF EPA COMMENTS

The sponsor, the Phosphite Producers HPV Consortium (PPHC), submitted Robust Summary information dated May 31, 2000 to EPA and posted a test plan to the HPV Tracking System Web site (www.hpvchallenge.com). EPA posted the cover letter and robust summary submission on the ChemRTK Web site on June 13, 2000. The proposed information-gathering plan is for *tris*(Nonylphenyl) phosphite (CAS # 26523-78-4).

EPA has reviewed this submission and has reached the following conclusions:

1. The submission comprises a minimally acceptable test plan overall.

2. Chemical characterization. A brief statement of the uses of the chemical would help reviewers assess the appropriateness of some of the proposed tests.

3. Proposed health endpoint testing: Acute toxicity. Because adequate summaries were submitted for acute oral toxicity, EPA believes no further acute toxicity studies are needed for the purposes of the U.S. HPV Challenge Program.

4. Proposed health endpoint testing: Repeat dose toxicity. Sufficient information has been provided for this endpoint. Therefore, in place of the proposed combined repeat dose/reproductive/developmental toxicity screening test (OECD Test Guideline 422), the combined reproductive/developmental toxicity screening test (OECD Test Guideline 421) is an acceptable alternative.

5. Proposed health endpoint testing: Developmental toxicity. The proposal includes conducting a combined repeat dose/reproductive/developmental toxicity screening test (OECD Test Guideline 422) in addition to a pre-natal developmental toxicity test (OECD 414). There is no rationale presented for conducting both tests. The OECD 421 screening study identified above is sufficient to cover the reproductive and developmental toxicity endpoints for the purposes of the U.S. HPV Challenge Program.

6. Proposed health endpoint testing: General. The sponsor proposes to perform testing beyond the recommendations of the U.S. HPV Challenge Program. EPA presumes that these tests may be needed for purposes outside of the U.S. HPV Challenge Program. See comments on this issue from the sponsor under “Letter of Clarification” for this submission on this Web site.

7. Ecotoxicity Studies, Acute Aquatic Toxicity. The submitted test data summaries for fish, daphnia, and green algae could not be adequately evaluated because certain information was not reported. The information in the full study report may address some of the issues identified.

8. Fate. The model to be used is not specified. EPA recommends that the EQC Level III model be used to estimate transport and distribution for the purposes of the U.S. HPV Challenge Program.

EPA COMMENTS ON THE TRIS(NONYLPHENYL) PHOSPHITE CHALLENGE SUBMISSION

GENERAL

The sponsor supplied a minimally acceptable package. However, the test plan on the industry HPV Tracking System Web site and the test plan summary table presented preceding the robust summaries submitted to EPA did not always agree (see below for details).

There was no statement about the general use of the HPV chemical, which makes it difficult to assess the appropriateness of some of the proposed tests (e.g., whether there is a need to conduct the acute dermal toxicity test proposed by the sponsor).

TEST PLAN

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

Data were submitted for vapor pressure. The sponsor's approach for the remaining endpoints should satisfy the needs of the U.S. HPV Challenge Program.

Fate (photodegradation, stability in water, biodegradation, and transport/distribution).

EPA believes the sponsor's approach should satisfy these endpoints. However, the test plan does not specify the model to be used for transport/distribution estimation. EPA prefers the EQC Level III fugacity model (available free from http://www.trentu.ca/academic/aminss/envmodel/) for the U.S. HPV Challenge Program.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

EPA believes the sponsor's approach should satisfy these endpoints. However, EPA also notes:

Proposed health endpoint testing: Acute toxicity. There is a discrepancy between the test plan summary sent to the EPA and posted on the EPA Web site and the test plan posted on the industry tracker at www.hpvchallenge.com. The former proposes to perform inhalation and dermal acute toxicity studies and the latter proposes not to conduct any further acute toxicity testing. Because adequate summaries were submitted for acute oral toxicity, no further acute toxicity studies are needed for the purposes of the U.S. HPV Challenge Program.

Proposed health endpoint testing: Repeat dose toxicity. Sufficient information has been provided for this endpoint. Therefore, there is no need to perform the proposed combined repeat-dose/reproductive/developmental toxicity screening test (OECD Test Guideline 422). An alternative is to conduct the combined reproductive/developmental toxicity screening test (OECD Test Guideline 421).

Proposed health endpoint testing: Genotoxicity. EPA notes another discrepancy between the test plan summary sent to the EPA and posted on the EPA Web site and the test plan posted on the industry tracker at www.hpvchallenge.com. The former proposes to conduct another *Salmonella* assay on the HPV chemical whereas the latter does not. EPA's position is that the robust summary submitted for this endpoint is not adequate for the purposes of the U.S. HPV Challenge Program and so there is a need to repeat the study. In addition, the sponsor is proposing to conduct an in vivo genotoxicity study which is beyond the needs of the U.S. HPV Challenge Program. The sponsor presented no rationale for conducting the *in vivo* genotoxicity study.

Proposed health endpoint testing: Developmental toxicity. The proposal includes conducting a combined repeat dose/reproductive/developmental toxicity screening test (OECD Test Guideline 422) in addition to a pre-natal developmental toxicity test (OECD 414). There is no rationale presented for conducting both tests. The OECD 421 screening study is sufficient to cover the reproductive and developmental toxicity endpoints for the purposes of the U.S. HPV Challenge Program.

Ecological Effects. EPA was unable to evaluate the adequacy of the available data because of omissions from the data summaries (see specific comments, below). EPA reserves further comment on these studies pending results of the planned water solubility testing.

SPECIFIC COMMENTS ON ROBUST SUMMARIES

EPA evaluations are based on the guidance document available at http:\\www.epa.gov/opptintr/chemrtk/guidocs.htm.

Chemistry

EPA evaluated the robust summary submitted for vapor pressure and found it adequate for the purposes of the U.S. HPV Challenge Program.

Health Effects

EPA evaluated nine health endpoint robust summaries and found six to be adequate for the purposes of the U.S. HPV Challenge Program. The exceptions were the *Salmonella,* reproductive toxicity, and developmental toxicity summaries presented below. The following comments are provided and reflect the information in the robust summary (the full study report may address these comments):

Acute Toxicity. There were three robust summaries submitted for acute oral toxicity. The first two (Unpublished, 1957, 1965) appear to have enough information to be considered adequate in the U.S. HPV Challenge Program, whereas the other (Majlathova, 1981) is missing important information (number of animals, doses used, strains of rat/mouse used, observation period).
Repeat Dose Toxicity. There were three robust summaries submitted for repeat dose toxicity: 90-day and two-year studies with rats and a two-year study with dogs. In all three studies the route of exposure was oral via the diet. Although all three studies were performed before GLPs were in place (1957 and 1961 for the 90-day and two-year studies, respectively), the summaries appear adequate for the purposes of the U.S. HPV Challenge Program.

Genotoxicity Studies. The summary is considered inadequate because the following information was not listed: (1) the method; (2) the individual doses used; (3) there was no information on the cytotoxicity of the test material; (4) the number of replicates per concentration or whether the test was repeated; (5) the type of inducer used to prepare the S9 fraction; and (3) the criteria used to judge whether the chemical was positive or negative.

Reproductive Toxicity. The sponsor included a robust summary of the two-year rat study described above in the repeat dose toxicity section. This study had a reproductive toxicity component in its design, however, there was not enough information in the robust summary to consider it adequate for this endpoint in the U.S. HPV Challenge Program. The following information was not presented: (1) methodology related to the reproductive toxicity portion of the test; (2) the premating, mating, and post-mating dosing regimen; (3) method of determining proof of pregnancy; (4) the exact number of animals that were pregnant and gave birth, and the associated number of pups; (5) how mating occurred to produce the second generation of offspring; and (6) detailed results by generation.

Developmental Toxicity. A summary of an in-vitro developmental toxicity study with chick embryos was presented. The study is not adequate or relevant to this endpoint for the U.S. HPV Challenge Program.

Ecotoxicity Studies

The comments below reflect the information presented in the robust summaries; information in the full study report may address some of the issues identified

Aquatic Toxicity. Robust summaries were submitted for acute studies on fish, daphnia, and green algae (one study summary for each organism).

The submitted test data for fish, daphnia, and green algae could not be adequately evaluated because of the following deficiencies in reporting:

1) The composition of the test material was not reported. The material was identified only by product name with no analytical data.

2) The predicted log P value of 20 indicates a much lower water solubility than the reported EC50. Information on the preparation of stock solution was not given, such as use of a carrier solvent, and whether it was determined that the substance was dissolved and not merely dispersed.